The opinion in support of the decision being entered today is not binding precedent of the Board.

Paper ~~50~~ 26

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

ISH K. **KHANNA**,
RICHARD M. WEIER, and YI YU

Junior Party
(Patent No. 5,935,990)[1],

v.

TOMIO **KIMURA**,
YASUO NOGUCHI, AKIRA NAKAO, KEISUKE SUZUKI,
SHIGERU USHIYAMA, AKIHIRO KAWARA and MASAAKI MIYAMOTO

Senior Party
(Application 09/678,218)[2].

Patent Interference 105,103 (NAGUMO)

Before: LEE, LANE, and NAGUMO, Administrative Patent Judges.

NAGUMO, Administrative Patent Judge

DECISION ON PRELIMINARY MOTIONS

[1] Based on application 08/987,356, filed on December 9, 1997. Accorded benefit for priority of provisional application 60/032,688, filed December 10, 1996. The real party in interest is G.D. Searle, Inc., a wholly owned subsidiary of Pharmacia Corp., which is a wholly owned subsidiary of Pfizer Inc.

[2] Reissue application 09/678,218, filed September 29, 2000, based on U.S. Patent 5,908,858, which is based on application 08/824,775, filed March 26, 1997. Accorded benefit for priority of JP 8-083,562, filed April 5, 1996. The real party in interest is Sankyo Co., Ltd.

This is a decision and memorandum regarding two preliminary motions filed by senior party Kimura. Junior party Khanna has not filed any preliminary motions. (Paper 25).

An oral hearing was held before a court reporter on 11 March 2004. (Transcript, Paper 49.)

Joseph M. Skerpon, Esq., argued for Junior party Khanna. Herbert Goodman, Esq., argued for Senior party Kimura.

I. Introduction

This interference relates to substituted pyrrolyl compounds that are said to be useful for treating cyclooxygenase-2 ("COX-2") mediated disorders. In lay terms, such drugs are useful for treating pain, fever, and inflammation without the stomach upset often associated with aspirin.

II. Findings of fact

The record supports the following findings of fact, as well as other findings of fact set forth in the discussion, by a preponderance of the evidence.

The parties

Khanna

1. Khanna involved patent 5,935,990 ("990 patent") is based on application 08/987,356, which was filed on 9 December

1997. (KhaX 2001.)[3]

2. The Khanna 990 patent claims the benefit under 35 U.S.C. § 119(e) of provisional application 60/032,688, filed December 10, 1996.

3. Khanna has been accorded benefit for priority of provisional application 60/032,688, filed December 10, 1996. (Paper 1 at 3.)

4. The named inventors of the Khanna patent are Ish K. Khanna, Richard M. Weier, and Yi Yu.

5. The real party in interest is G.D. Searle, Inc., a wholly owned subsidiary of Pharmacia Corp., which is a wholly owned subsidiary of Pfizer Inc.

Kimura

6. Kimura is involved on the basis of reissue application 09/678,218, filed September 29, 2000, based on U.S. Patent 5,908,858 (KhaX 2002), which issued from application 08/824,775, filed March 26, 1997.

7. Kimura's 858 patent claims the benefit under 35 U.S.C. § 119(a) of Japanese patent application JP 8-083,562, filed April 5, 1996.

8. Kimura has been accorded the benefit for priority of

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[3] Khanna exhibits are referred to as "KhaX 2___."
Kimura exhibits are referred to as "KimX 1___."

JP 8-083,562, filed April 5, 1996. (Paper 1 at 4.)

9. Kimura's real party in interest is Sankyo Co., Ltd.

The count

10. Count 1, the sole count in this interference, is:

The compound as defined by claim 1 of Khanna's 5,935,990 patent,

or

the compound as defined by claim 13 of Kimura's 09/678,218 application.

11. The claims of the parties are:

Khanna 1-31

Kimura 13-24, 28, 29, 31-33, 35-37, 40, 41, 43-86.

12. The claims of the parties that correspond to Count 1 and that are therefore involved in this interference are:

Khanna 1-4, 6-13, 15-22, 24-31

Kimura 13-24, 28, 29, 31-33, 35-37, 40, 41, 43-86.

13. The claims of the parties that do not correspond to Count 1, and therefore are not involved in the interference, are:

Khanna 5, 14, 23

Kimura none.

The claims

Khanna claim 1 and Kimura claim 13 are reproduced in the appendix attached to this motion. The following summary is provided to orient the reader to Khanna's claims, which are the

focus of this decision.

Khanna's claims cover a class of 1,2,4,5-tetrasubstituted pyrroles, which in Khanna's terminology are represented by Formula I (KhaX 2001 at col. 46, ll. 50-58), which is generic to, or encompasses, Khanna's Formula II and Formula III. Formula I is recited in claim 1, and further limited in claims 2 and 3.

Compounds of Formula II (KhaX 2001 at col. 49, ll. 10-20) have a methylsulfonylphenyl (H_3C-SO_2-phenyl-) or aminosulfonylphenyl[4] (H_2N-SO_2-phenyl-) group at position 2, on the carbon adjacent to the pyrrole nitrogen. These compounds may have, but are not required to have hydrogen at position 5. Khanna Formula II is recited in claim 6, and is further limited in claim 7.

Compounds of Formula III (KhaX 2001 at col. 49, ll. 50-60) have the methyl- or amino-sulfonylphenyl groups at position 1, on the pyrrole nitrogen. These compounds are required to have hydrogen at position 5. Khanna Formula III is recited in claim 8, and further limited in claim 9.

Khanna's claimed compounds avoid a prior art reference, German patent DE 1,938,904, by requiring that when the substituent on the pyrrole nitrogen is methyl- or amino-

[4] Kimura refers to this group as "sulfamoyl"; it is also called "sulfamido" by a German prior art reference.

sulfonylphenyl, the substituent R_3 must be hydrogen.

The motions

14. Two motions filed by Kimura are before us for decision[5]:

a. Kimura preliminary motion 2, for judgment that all of Khanna's involved claims are obvious over prior art. (Paper 26; Opp Paper 32, errata Paper 34; Reply Paper 36.)

b. Kimura preliminary motion 3, to designate certain of Kimura's claims as not corresponding to the Count. (Paper 27; Opp Paper 33; Reply Paper 51.)

III. Discussion

Kimura preliminary motion 2

the prima facie case

15. Kimura urges in its principal brief that Khanna claims 1-4, 6-13, 15-22, and 4-31 were "obvious (structurally and biologically) for the reasons set forth in III.A.12. through III.A.16." (Paper 26 at 23.)

16. At III.A.12., Kimura states that the subject matter of each of the Khanna claims was obvious "(structurally and biologically) . . . over the disclosure of DE 1938904 in

[5] Kimura miscellaneous motion 1 (Paper 13), was granted (Paper 14). Kimura miscellaneous motion 4, seeking an order directing Khanna to return samples of compounds that Kimura provided to Khanna for testing (Paper 44; Opp. Paper 45; Reply Paper 46) was granted at oral hearing. (Paper 49 at 69.)

combination with the disclosure of USP 5,521,213 (Exhibit 1006, p. 8, l. 20 through p. 9, l. 6)." (Paper 26 at 7.)

a. DE 1,938,904 ("DE 904") is a German "laid open" patent document, entitled *1-Phenylpyrrols*, published 5 February 1970. (KimX 1007; KimX 1008 is the English translation.)

b. DE 904 relates to compounds having a substituted phenyl group at the 1-position (i.e., on the ring nitrogen) and methyl or certain substituted phenyl groups at the ring carbons adjacent to the ring nitrogen. (KimX 1008 at 2.)

c. The compounds are disclosed as having analgesic (pain-relieving) properties, which were demonstrated in mice for certain examples. (KimX 1008 at 18.)

d. DE 904 discloses the compound 1-para-sulfamidophenyl-2-methyl-5-phenyl-pyrrol, referred to *post* as "GPC-0," and as "the German compound." (KimX 1007 at 13, "Beispiel 18"; KimX 1008 at 11-12, Example 18.)

e. United States Patent 5,521,213 ("*Prasit 213*") was issued to Petpiboon Prasit et al., and is titled *Diaryl bicyclic heterocycles as inhibitors of cyclooxygenase-2*. (KimX 1013.) *Prasit 213* was issued 28 May 1996, based on application 297,461, filed 29 August 1994.

17. At III.A.13., Kimura states that the subject matter of each of the Khanna claims was obvious "(structurally and

biologically) . . . over the disclosure of DE 1938904 in combination with the disclosure of USP 5,550,142 (Exhibit 1006, p. 8, l. 20 through p. 9, l. 6)." (Paper 26 at 7.)

a. United States Patent 5,550,142 ("*Ducharme*") was issued to Yves Ducharme et al., and is titled *Phenyl heterocycles as COX-2 inhibitors*. (KimX 1014.) *Ducharme* issued on 27 August 1996, based on application 438,130, filed 8 May 1995, which is a division of application 179,467, filed 10 January 1994, now U.S. Pat. 5,474,995, which is a continuation-in-part of application 082,196, filed 24 June 1993, abandoned.

18. At III.A.14., Kimura states that the compounds claimed by Khanna were structurally obvious, and that "[i]t was also obvious that the compounds within the scope of said claims are a class of compounds which should have some degree of anti-inflammatory and analgesic activity, although the degree of such activity could only be determined by *in vivo* testing (Exhibit 1006, p. 9, ll. 7 and 15)." (Paper 26 at 7.)

19. At III.A.15., Kimura explains that each of *DE 904*, *Prasit 213*, and *Ducharme* "discloses pharmaceutical compositions containing structurally related compounds for the same medical use (Exhibit 1006, p. 9, ll. 16-23)." (Paper 26 at 7.)

20. At III.A.16., Kimura elaborates that the methods of treating COX-2 mediated disorders recited in Khanna claims 19-22

and 24-31 were obvious over the "disclosure of the same medical use in said prior art and the structural obviousness of the compounds specified in said method claims." (paper 26 at 8.)

21. Exhibit 1006 is a declaration by Hiroaki Yanagisawa ("Yanagisawa").

22. Yanagisawa states that he is President of Chemtech. Labo., Inc., a subsidiary of Sankyo Co., Ltd, and a visiting professor at the School of Pharmaceutical Sciences, University of Tokyo. (KimX 1006 at 1, ¶I.2.(iii).)

23. Yanagisawa states that he holds a doctoral degree from Keio University based on studies of the synthesis of cyclic α-amino acids, and that he has been engaged in medicinal chemistry research since 1970, particularly in the area of antibiotics and anti-hypertension agents. (KimX 1006 at 1, ¶¶I.1. and I.2.(i).)

24. Yanagisawa highlights the disclosure in DE 904 of the compound 1-para-sulfamoylphenyl-2-methyl-5-phenyl-pyrrole. (KimX 1006 at 4, V.1.)

a. Based on his statement in IV.2. referring to "the German compound identified in DE 1938904 ("DE 904") discussed in the following paragraph" (KimX 1006 at 4), we understand Yanagisawa to refer to this compound as "the German compound" throughout his declaration.

b. According to Yanagisawa, DE 904 teaches that the disclosed compounds have analgesic and anti-inflammatory activity. (*Id.* at V.2.)

c. Yanagisawa further states that DE 904 discloses pharmaceutical compositions containing the disclosed compounds as active ingredients. (*Id.* at V.3.)

Consideration of DE 904 (KimX 1007; translation KimX 1008) confirms Yanagisawa's representations.

25. According to Yanagisawa, the compounds claimed by Khanna differ from the compound disclosed in DE 904 in that "[t]he German compound falls within the scope of the Khanna Formula III except that the position adjacent the 1-pyrrole group which is methyl in the German compound is defined as hydrogen in USP 5,935,990, thereby excluding the German compound." (KimX 1006 at 7, VI.1.)

26. Yanagisawa states further that *Khanna 990* claims compounds containing the aminosulfonylphenyl group [H_2N-SO_2-phenyl-] and the methylsulfonylphenyl [H_3C-SO_2-phenyl-] group in the alternative. (KimX 1006 at 7, VI.2.)

a. According to Yanagisawa, medicinal chemists recognize aminosulfonylphenyl and methylsulfonylphenyl as "bioisosteres." (*Id.*)

b. Yanagisawa states that bioisosteres "have almost

the same chemical structural profile and biological activity" (*id.*), and cites disclosure of compounds in references of record, including *Ducharme*, *Prasit 213*, and *Reitz*[6] having either group as alternative substituents as evidence of recognition among medicinal chemists of the biological equivalence of aminosulfonylphenyl and methylsulfonylphenyl. (*Id.* at 7-8.)

27. According to Yanagisawa, a further difference between the *Khanna 990* compounds and the German compound is that:

> whereas the German compound has the aminosulfonylphenyl substituent in the 1-pyrrole position [i.e., attached to the ring nitrogen atom] with the second phenyl substituent in the 2-position [i.e., attached to the ring carbon adjacent to the ring nitrogen], the [Khanna] claims (i) cover said 1-pyrrole compounds (generic to the German compound) and (ii) also cover compounds in which the amino(or methyl)sulfonylphenyl substituent is in the 2-position, and the second phenyl substituent is in the 1-pyrrole position.

(KimX 1006 at 8, VI.3.)

Yanagisawa's statement (i) is not accurate. As Yanagisawa stated previously, the Khanna 990 compounds represented by formula III, in which the amino(or methyl)sulfonylphenyl group is attached to the pyrrole nitrogen, exclude the German compound because the substituent at the 5-position cannot be methyl.

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[6] David B. Reitz et al., *Selective cyclooxygenase inhibitors: novel 1,2-diarylcyclopentenes are potent and orally active COX-2 inhibitors*, 37 J. MED. CHEM. 3878 (1994). ("*Reitz*," KimX 1009.)

(KimX 1006 at 4, IV.2.) Thus, Khanna claims 8 and 9 are not generic to the German compound.

a. Yanagisawa urges that "the equivalence of the two structures (illustrated in paragraph IV.1.) [i.e., formulas II and III] is made obvious" by the disclosures in the art relied on by Kimura in its motion[7], as well as by *Reitz*, "which points up the importance of the adjacent relationship of the two phenyl groups on the central ring of three different 5-member ring systems." (KimX 1006 at 8, VI.3.)

28. Yanagisawa argues, in declaration paragraph VI.4 (KimX 1006 at 8, l. 20, to 9, l. 6), that the subject matter of *Khanna 990* "was obvious (structurally and biologically)" over the disclosure of *DE 904* in combination with the disclosure of either *Prasit 213* or *Ducharme*. (KimX 1006 at 8., VI.4., ll. 20-22.)

a. Yanagisawa explains that "[e]ach of said United States patents discloses a central pyrrole ring having a phenyl substituent on the 2-position and the 3-position and also discloses that either of said phenyl groups may be a 4-aminosulfonylpheny[l] or a 4-methylsulfonylphenyl." (KimX 1006

[7] Yanagisawa also summarizes the disclosure of WO96/03392 (a WIPO patent to Talley et al.) at KimX 1006, 6, V.7., and refers to this document at KimX 1006, 8, VI.3. Kimura does not cite this document in its principal brief at 23, IV.B. or IV.B.1., or at 7-9, III.A.12. through III.A.16. Accordingly, we shall not consider this disclosure. Kimura's style of argument verges on incorporation of the Yanagisawa declaration by reference, a practice that we do not condone. See Standing Order § 13 (Paper 2).

at 8, ll. 30-34.)

b. Yanagisawa argues that the common disclosure that such compounds are useful for the treatment of arthritis, inflamation, pain, etc., "would have led workers in the field to combine the teaching in these references of compound(s) with a 5-membered heterocyclic ring and adjacent diphenyl substituents with one of the substituents being a 4-aminosulfonylphenyl or a 4-methylsulfonylphenyl and the teaching that all of said compounds have analgesic and anti-inflammatory activity." (KimX 1006 at 8, l. 34, to 9, l. 6.)

29. Yanagisawa does not identify differences between compounds in *Prasit 213*, *Ducharme*, or *Reitz*, and compounds encompassed by Kimura's claims.

discussion

The burden is on Kimura, as the moving party, to establish in its principal brief the obviousness of the subject matter of Khanna's involved claims over the cited prior art. 37 CFR § 1.637(a); *Velander v. Garner*, 348 F.3d 1359, 1369-70, 68 USPQ2d 1769, 1777 (Fed. Cir. 2003).

As an initial matter, Khanna urges that Kimura has used impermissible hindsight to select the compound GPC-0 from the "broad genus" disclosed by DE 904. (Khanna opposition 2, Paper 32 at 15.) According to Khanna, there is no motivation to

select GPC-0 because it was not tested for biological activity, and further, because the single compound (out of four) having a 1-para-aminosulfonylphenyl ("1-PASP") substituent was not a very active compound compared to the compounds that were tested in DE 904. (Paper 32 at 15.) The generic description of utility at page 36 of the translation of DE 904, according to Khanna, provides "absolutely no suggestion in the German patent that GPC-0 in particular has desirable anti-inflammatory activity." (Paper 32 at 16.)

We do not agree. Our conclusion might be different if DE 904 had neither exemplified GPC-0 nor tested any 1-PASP compounds, and if Kimura had merely selected that compound from the generic disclosure of substituted 1-phenylpyrroles in DE 904. However, DE 904 specifically reported the synthesis of the compound GPC-0. (KimX 1007 at 13, example 18.) Moreover, as Khanna admits (Paper 32 at 8-9, ¶6, and at 15), DE 904 reports that a compound having the same 1-PASP substituent was tested and showed some activity. (KimX 1007 at 43, Table II, second entry, reporting toxicity data; at 64, Table VI, second entry, reporting pain reduction.) Together with the teachings of utility in German patent document DE 904, these specific teachings provides notice to the ordinary medicinal chemist that a class of compounds, and GPC-0 in particular, is of interest "for treatment

of painful and inflammatory ailments." (KimX 1008 at 36.) Accordingly, we find that the ordinary worker would have found motivation to consider modifying the disclosed compound GPC-0.

Khanna argues further that there is no motivation to select GPC-0 for modification because GPC-0 has very low COX-2 inhibiting activity. (Paper 32 at 19.) In Khanna's words, "[s]imply put, one skilled in the art would not have had a reasonable expectation that modifying a marginally active compounds, such as GPC-0, would result in a potent and selective COX-2 inhibitor." (Paper 32 at 20.) The flaw in this argument is that the ordinary worker only needs to have a reasonable expectation of obtaining a compound that has some anti-inflammatory or analgesic properties; one need not have any expectation of obtaining a "potent and selective COX-2 inhibitor." Khanna does not deny that the compound tested in DE 904 as well as compound GPC-0 exhibit some anti-inflammatory or analgesic properties. Given that GPC-0 exhibits modest properties in those regards, evidence that compounds that are *prima facie* obvious over GPC-0 are potent and selective COX-2 inhibitors would be strong evidence of unexpected results. That is a distinct inquiry that we shall delay until a prima facie case of obviousness has been established.

Kimura argues, correctly, that a claim that encompasses

compounds that are obvious in view of the prior art is unpatentable. (Paper 26 at 22-23, ¶IV.A.3.) We accept Kimura's argument that its obviousness arguments are not limited to the "German compound," and that its arguments relate to all of the prior art on which it relies (Paper 36 at 10). We reject, however, any implication that its arguments are based on the structural similarities of prior art compounds depicted in Paper 36 at page 11, other than GPC-0, as Kimura did not identify in its principal brief the specific differences between any of these compounds and compounds of Khanna's invention, or how those differences would have been obvious to overcome. Such arguments were limited to Kimura's discussion of the compound GPC-0.

Although Kimura repeatedly asserts that Khanna's compounds are obvious "structurally and biologically," over the German compound, the evidence to which it points in support of its arguments is limited. We first address Kimura's argument regarding formula II. (Formula II is encompassed by Khanna compound claims 1-3, 5, and 6, but is recited specifically only in compound claims 5 and 6.) Initially, we agree that formula II encompasses compounds that differ from reference compound GPC-0 in the substitution of the PASP group at the 2-position, adjacent to the ring nitrogen, rather than at the 1-position, at the ring nitrogen. We note that such compounds have a methyl group at the

5-position and hydrogen at the 3- and 4- positions. We also agree that *Reitz*, *Ducharme*, and *Prasit 213* support the proposition that adjacent aryl substitution, relative to the double bond in a 5-membered ring, is an important structural feature that is related to the activity of cyclooxygenase inhibition. We note in particular the statement by *Reitz* that "[i]t was believed that the function of the heterocyclic ring was to provide the necessary double bond geometry and that the heterocycle itself was not essential for good activity." (KimX 1009 at 3878, col. 2.) Both *Reitz* and *Ducharme* provide examples of "1,2-diaryl" substituted 5-membered ring compounds that show some inhibition of swelling and pain that are characteristic of cyclooxygenase inhibition. *Prasit 213* provides examples in indole systems, in which the 1,2-diaryl moieties are adjacent substituents on the 5-membered nitrogen heterocyclic ring that is fused to the 6-membered ring. Although *Prasit 213* supports *Reitz*, the relevance to pyrrole systems is less clear, as Kimura does not explain the influence of the fused ring on the physiological properties of the compounds. Although Khanna appears to be correct when it argues that no 1,2-diaryl pyrroles are of record (Paper 32 at 23), the express teaching of *Reitz* is that the identity of the atoms that make up the 5-membered ring is not critical. We find that this teaching motivates the

combination of the references.

Khanna argues that the patentability of the 990 patent claims over *DE 904* "has already been considered and decided" [by the examiner]. (Paper 32 at 13.) Similarly, Khanna asserts that patentability over *Ducharme* has already been decided. (Paper 32 at 23.) These arguments have no merit. First, the examiner's determinations are not binding, although they may have some persuasive value. Second, the only evidence Khanna points to is the indication on the cover of the 990 patent that the two documents were considered. Khanna points to no commentary by the examiner during prosecution, which is not surprising, as the examiner indicated allowability of all the claims, without comment, on the first action on the merits. (Application 08/987,356, Paper 7.) The examiner's silence as to a particular combination of references that was never highlighted has little if any persuasive force.

As Kimura is careful to point out, the degree of activity for any particular compound does not appear to be predictable, but some activity is expected. (Paper 26 at 7, III.A.14., citing Yanagisawa, KimX 1006 at 9, ll. 7 and 15.) Moreover, *Ducharme* provides an example of pairs of compounds in which an aminosulfonylphenyl group is adjacent to a phenyl group in both 1,2- and 2,1-orientation on five-membered heterocyclic rings, in

which both compounds show some degree of swelling or pain inhibition. Compare KimX 1014, second compound in col. 52, with the second compound in col. 53. Khanna points to an article by Prasit[8] ("*Prasit 1999*"; KhaX 2003) as evidence that 1-,2-diaryl-substituted 5-membered heterocyclic ring compounds are not necessarily biologically equivalent. (Paper 32 at 23-24.) According to *Prasit 1999*, lactones **2** and **3** differ only in the relative positions of the adjacent substituted phenyl groups on the 5-membered lactone ring, but "[t]he lactone **2** was found to be *essentially inactive*, only **3** was found to have significant inhibitory activity against COX-2." (KhaX 2003 at 1774; emphasis added.) *Prasit 1999*, however, post-dates Khanna's filing date, and Khanna does not point to any evidence that *Prasit 1999* relates to the state of the art at the time of Khanna's invention of the claimed subject matter. *See, e.g., In re Wright*, 999 F.2d 1557, 1563 n.8, 27 USPQ2d 1510, 1514 n.8 (Fed. Cir. 1993) (emphasizing that the critical date is the time the invention was made). We therefore accord *Prasit 1999* little weight.

Khanna argues that compounds of formula II are "even further removed [than compounds of formula III] from any compound within

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[8] P. Prasit et al., *The discovery of rofecoxib, [MK 966, VIOXX®, 4-(4'-methanesulfonylphenyl)-3-phenyl-2(5h)-furanone], an orally active cyclooxygenase-2 inhibitor*, 9 BIOORGANIC & MEDICINAL CHEM. LETT. 1773 (1999).

the scope of the German patent." (Paper 32 at 16.) There is, according to Khanna, no teaching in DE 904 suggesting that the phenyl on the ring carbon adjacent to the ring nitrogen be substituted with an amino- or methyl-sulfonyl group. (*Id.*) This argument overlooks the teachings of *Prasit 213*, *Ducharme*, and *Reitz*, regarding the interchangeability of 1,2-phenyl substituents in such systems. Khanna cannot attack the gaps in the teachings of the references individually, because it is the combined teachings that must be considered in the evaluation of obviousness. *Cable Electric Products, Inc. v. Genmark, Inc.*, 770 F.2d 1015, 1025, 226 USPQ 876, 887-86 (Fed. Cir. 1985) ("the suggestion to modify the art to produce the claimed invention need not be expressly stated in one or all of the references used to show obviousness. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.") (internal quotes and citation omitted.)

On this record, we conclude that the preponderance of the evidence indicates that, as of Khanna's filing date, one of ordinary skill in the art would have had a reasonable expectation of successfully obtaining analgesic compounds when exchanging the 1-phenyl substituent for the 2-phenyl substituent in compounds such as GPC-0. Accordingly, we hold that the modification of

"exchanging" the 1-PASP and the 2-phenyl groups in compound GPC-0 would have been obvious to the ordinary medicinal chemist, and that Kimura has established a *prima facie* case that certain compounds within the scope of Khanna formula II would have been obvious in view of the GPC-0 compound and the other teachings in the art.

The *prima facie* case for the obviousness of compounds of formula III stands differently. (Formula III is encompassed by compound claims 1-3, 8, and 9, but is recited specifically only in claims 8 and 9.) Kimura has identified the difference between the *DE 904* compound GPC-0 and compounds within the scope of Khanna Formula III to be the replacement, in Khanna Formula III, of the 5-methyl group by hydrogen. (Paper 26 at 6, III.A.9.) Kimura has not, in its principal brief, directed our attention to any testimony or other evidence of record that one of ordinary skill in the art would have been motivated to substitute hydrogen for methyl at the pyrrole 5-position in compound GPC-0. Nor has Kimura directed us to evidence in the record regarding the basis one would have had to expect, reasonably, that such a substitution would result in a compound having analgesic or anti-inflammatory properties. Rather, Kimura has merely stated the legal conclusion that compounds within the scope of formula III are structurally obvious over GPC-0. We decline to weigh, in the

first instance, whether data reported in the various references described by Yanagisawa and the other experts tends to favor or disfavor facts that have been, at best, implied. Not having been confronted with such an argument, Khanna has not had a full and fair opportunity to challenge that evidence.

Kimura argues that the prior art shows that "[t]he equivalence of the two structures, i.e., of formula II and formula III, is made obvious by the disclosure in each of [*Prasit 213*] (Exhibit 1013), and [*Ducharme*] (Exhibit 1014) . . . that in their compounds, either of the adjacent two phenyl substituents may be the phenyl substituent having the sulfonyl substituent." (Paper 26 at 6, III.A.11.) However, whether formula III structures are obvious over formula II structures (or vice-versa) is irrelevant in the present inquiry because neither is available as prior art with respect to the other.

The flaw in Kimura's argument is the absence, in its principal brief, of evidence and argument based on that evidence that replacement of the 5-methyl group from GPC-0 would have been obvious. Similarly, Kimura's implicit argument that substitution at positions 3- and 4- of GPC-0 would have been obvious lacks an adequate evidentiary foundation. Kimura cites *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977) for the proposition that "[c]hemical compounds which have close structural similarities

and similar utilities are not patentable because they are obvious in the absence of an unexpected activity that supports patentability." (Paper 26 at 22, IV.A.1.) Indeed, the court in *Wilder* stated that "one who claims a compound, which is structurally similar to a prior art compound must rebut the presumed expectation that the structurally similar compounds have similar properties." 563 F.2d at 460, 195 USPQ at 429; *quoted* in *In re May*, 574 F.2d 1082, 1094, 197 USPQ 601, 611 (CCPA 1978) (explaining that "implicit in Wilder II is that an applicant may rebut the aforementioned presumption by producing sufficient evidence which demonstrates a substantial degree of unpredictability in the pertinent art area.") The CCPA had previously explained, however, that "[t]he term 'presumption of unpatentability,' as it is used in the Henze case, refers to an inference of fact." *In re Mills*, 281 F.2d 218, 222, 126 USPQ 513, 516 (CCPA 1960) (footnote omitted, underscore added). Rather than a 'legal presumption,' the 'inference of fact' was that "the adjacent homologue of the known chemical compound [i.e., a compound that differed by one $-CH_2-$ group from the known compound] was unpatentable, and that such inference of fact placed the burden of persuasion on the applicant who asserted the contrary." 281 F.2d at 223, 126 USPQ at 517. The court then explained the consequences for anyone attempting to rely on a

chemical theory such as homology or any other form of structural similarity in the chemical arts:

> If the [movant] wishes to rest a rejection on chemical theory, it is its duty to support its case with adequate evidence of the existence and meaning of that theory. Homology provides for the chemist a convenient system of structural classification. Inherent in that system are differences as well as similarities in the properties and reactions of the members of any given homologous series.
>
> A chemist, and it is from the standpoint of a chemist skilled in this art that the question of obviousness must be resolved, would consider the differences as well as the similarities in the properties and reactions of the members of any given homologous series. He also would consider that in the case of adjacent homologues similarities would be more likely than where the homologues are farther apart in the series. The 'legal presumption' as here applied by the board precludes making the factual evaluation which a chemist would make in a case such as the present. **Homology per se should, therefore, be treated as a chemist would treat it, being nothing more than a fact which must be considered with all other relevant facts before arriving at the conclusion of 'obviousness' specified in 35 U.S.C. 103.**

281 F.2d at 223-24, 126 USPQ at 517-18 (emphasis added). The 'fact' of structural similarity is specific to the circumstances of each case, and must, in an interference, be established by appropriate evidence. 37 CFR § 1.671. The Federal Circuit has repeatedly cautioned that "generalization is to be avoided insofar as specific structures are alleged to be *prima facie* obvious one from the other." *In re Jones*, 958 F.2d 347, 350, 21

USPQ2d 1941, 1943 (Fed. Cir. 1992), *citing In re Grabiak*, 769 F.2d 729, 731, 226 USPQ 870, 872 (Fed. Cir. 1985). For that reason, Kimura's belated reliance in its reply brief on *In re Druey*, 319 F.2d 237, 138 USPQ 39 (CCPA 1963) (finding, on that record, that replacement of hydrogen on a prior art pyrrole ring would have been obvious) is futile. As the Federal Circuit has noted, "[p]recedent cannot establish facts." *Case v. CPC Int'l, Inc.*, 730 F.2d 745, 750, 221 USPQ 196, 200 (Fed. Cir. 1984).

Accordingly, we hold that Kimura has not established a *prima facie* case of obviousness for compounds of Formula III.

We conclude that Kimura has established a *prima facie* case that variations of the compound GPC-0 in which the aminosulfonyl-phenyl group is at the 2-position and the phenyl group is at the 1-position would have been obvious. We emphasize that our findings are limited on the present record to modifications of GPC-0 that retain the methyl group at the 5-position, and that have hydrogen at the 3- and 4- positions. Kimura has failed to come forward with any evidence that methyl substitution at these positions would have been expected to result in de minimus changes in relevant chemical properties of these compounds.

In addition to claims to chemical compounds, Khanna has claims to pharmaceutical compositions and to methods of using the compounds and compositions to treat COX-2 mediated disorders.

The *DE 904*, *Ducharme*, and *Prasit 213* references are all directed towards compounds and compositions that are said to be useful for the treatment of pain and inflammation, which have been recognized for some time as COX-2 mediated conditions. Accordingly, if the compounds would have been obvious, so would the pharmaceutical compositions comprising such compounds, and the claimed methods of treatment using such compounds and compositions.

We hold that Kimura has established a *prima facie* case of obviousness of certain compounds of Formula II, and related compositions and uses, which are within the scope of Khanna involved claims 1-4, 6, 7, 10-13, 15, 16, 19-22, 24, 25, and 28-31. We hold further that Kimura has failed to establish a *prima facie* case of obviousness of any compounds or related subject matter within the scope of Khanna involved claims 8, 9, 17, 18, 26, and 27.

unexpected results

Khanna argues that the high COX-2 inhibiting activity of its claimed compounds and the selectivity of that inhibition relative to COX-1 are unexpected given the properties of compound GPC-0, and that any *prima facie* case of obviousness is therefore rebutted. (Paper 32 at 25-30.) In particular, Khanna points to

the IC_{50} properties[9], measured *in vitro*, of compounds KHA-1, KHA-8, KHA-9, KHA-10, KHA-11, KHA-13, KHA-18, KHA-20, KHA-22, and KHA-24, asserting that they have significantly higher potency than GPC-0, and high COX-2 selectivity. (Paper 32 at 26, citing the 990 patent, KhaX 2001, col. 44, Table II, and KhaX 2037, the Gierse declaration.)

Kimura argues that "[a]lthough Khanna and Kimura disclose *in vitro* screening for COX-2 selective inhibition, this property is not relevant unless the compound also has *in vivo* pharmacological efficacy. (The reverse is not true as can be understood from the fact that aspirin is highly useful but lacks COX-2 selectivity.)" (Paper 26 at 9, citing the Ushiyama declaration, KimX 1005 at 1-2, which recites identical language.) More particularly, Kimura argues that Khanna's set of compounds show similar low levels of *in vivo* analgesic and anti-edema properties as the compound GPC-0. (Paper 26 at 23, citing results of a swollen-paw pain test reported by Takayoshi Kojima, an expert witness for Kimura, KimX 1004.)[10] Kimura argues that because none of the

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[9] Khanna's expert Gierse defines IC_{50} as the concentration required to induce 50% inhibition of enzyme (COX-1 or COX-2) activity. (KhaX 2037 at 5, ¶8.) A test solution contains the enzyme, a dose of the test compound and a substrate (arachidonic acid). (*Id.* at 4-5, ¶7.) The amount of product (prostaglandin PGE_2) is measured after a set period of time (10 minutes). (*Id.*)

[10] According to Kojima, in this test ("Randall-Selitto"), rats are monitored for response to pain induced by injection of a saline suspension of Brewer's yeast into a paw. The yeast suspension induces inflammation.

tested compounds differs significantly in either *in vivo* test compared to the German compound, "none of said tested Khanna compounds have a property which can be characterized as an 'unexpected' activity or result. In the absence of such unexpected activity or result, each Khanna claim which includes within its scope at least one of said Khanna compounds is invalid." (Paper 26 at 24.)

Khanna responds that Kimura's *in vivo* tests are inadequate because they neglected to consider factors, in particular, the bioavailability of the compounds, that influence the *in vivo* efficacy of the compounds. (Paper 32 at 28.) Khanna's expert, Mark E. Smith ("Smith"), a Senior Research Advisor in Pharmacokinetics, Dynamics, and Metabolism at Pfizer, Inc., testified that ED_{50} values, such as those reported by Kojima, can be compared meaningfully only if similar bioavailability and plasma exposure are achieved. (KhaX 2041 at 3, ¶5.) Smith testified further that bioavailability depends on many factors, including "absorption, dissolution rates, hepatic extraction, free fraction in plasma, and even molecular weight," citing

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(KimX 1004 at 2, ¶2.) Five hours after a rat's paw was injected with the yeast suspension, the rat was given orally a solution of the test compound, and pain thresholds were measured at specified times thereafter. (KimX 1004 at 2-3, I.1.C1.)

several journal articles of record. (*Id.* at 3-4[11], ¶6.) Smith cites the observed free fraction in plasma of the drug candidate as a critical parameter. This is, according to Smith, the total measured plasma concentration not bound to carrier proteins (such as serum albumin), and it represents the fraction of the total dosage that is able to bind to the target of the drug. (*Id.* at 4, ¶7.) Moreover, Smith testifies that the mode of administration (oral, intravenous, subcutaneous, etc.) can affect the relative efficacy of the compounds. (*Id.* at 4-5, ¶8.)

Kimura replies that its *in vivo* tests are "the usual tests in this field to establish anti-inflammatory activity," citing their use in Khanna 990, US patent 5,466,823[12] (KimX 1020), and Smith's testimony that the tests are standard. (Paper 36 at 8.)

Khanna also criticizes the absence of compound KHA-9 from Kimura's analysis, arguing that KHA-9 is the compound closest to GPC-0, not KHA-8, which has an additional difference of a methylsulfonyl group on the 1-phenyl group, rather than an aminosulfonyl group, as in KHA-9 and GPC-0. (Paper 32 at 29-30.) Kimura responds to this criticism by contending that it does not

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[11] Page 4 was missing from all of the hard copies of KhaX 2041; we consulted the copy filed on the compact disk.

[12] U.S. Patent 5,466,823, issued to John J. Tally et al. on November 14, 1995, based on application 07/160,594, filed November 30, 1993, and assigned to G.D. Searle & Co., a party-in-interest of Khanna. This patent covers CELECOXIB®, a widely prescribed nonsteroidal anti-inflammatory drug.

consider KHA-9 to be unpatentable. (Paper 36 at 7.) Rather, Kimura argues that if any of the Khanna compounds do not have an unexpected activity, any claim at issue that reads on those compounds is invalid. (*Id.*) Kimura also notes that Khanna cites the unexpectedly high anti-edema activity of compound KHA-9 shown in Kimura's experiments as evidence of patentability. (*Id.* at 8, citing Paper 32 at 29-30.)

discussion

In order to reach the ultimate determination on the issue of obviousness, it is necessary to determine the weight to be accorded to evidence of both expected results and unexpected results. *In re May*, 574 F.2d 1082, 1092, 197 USPQ 601, 609 (CCPA 1978) (weighing expected potent analgesia against unexpected nonaddictive potent analgesia). Moreover, when comparing the properties of one compound against another, "[t]here is no basis in law for ignoring any property in making such a comparison." *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963) (holding that the failure of the board to consider biological or pharmaceutical properties of the claimed compounds as anti-inflammatory agents in the face of structural similarity was error). Indeed, the Federal Circuit has noted that, "[t]o be patentable, a compound need not excel over prior art compounds in all common properties. Evidence that a compound is unexpectedly

superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness." *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987) (citations omitted). As an initial matter, we observe that Kimura has based all of its obviousness arguments on the obviousness of the compound. (Paper 26 at 23.) Therefore, we shall not consider Khanna's claims for compositions or methods of using the compounds separately from the claims for the compounds.

Neither Kimura nor its expert Ushiyama explains why evidence of COX-2 selectivity based on *in vitro* testing is irrelevant to the issue of obviousness of the compounds claimed by Khanna. Although Kimura refers to "usefulness" in its principal brief (Paper 26 at 9, III.B.2.) and in its reply (Paper 36 at 8), the utility of the genus of compounds claimed by Khanna and by Kimura is not at issue in this proceeding, as neither party has moved that any claim is invalid for lack of compliance with 35 U.S.C. § 101. The record demonstrates that COX-2 selectivity was recognized, before Khanna's filing date, to be a critical aspect of the pharmacology of the claimed compounds. See, e.g., the Background section of *Prasit 213* (KimX 1013 at col. 1), citing an article published in NATURE in 1994 on the potential utility of COX-2 inhibitors. It appears that COX-2 selectivity is a necessary but not necessarily a sufficient property for ultimate

clinical use as a drug.[13] Such a conclusion is not surprising considering the complex interaction between various drugs and human physiology. When particular *in vitro* "properties of a compound," such as its interactions with two enzyme systems, are intimately related to the function of the compound *in vivo*, those *in vitro* properties are entitled to weight in the consideration of obviousness.

The parties dispute the significance of the *in vitro* results presented by Khanna's expert Gierse (KhaX 2037 at 7), by Table 1 of the Khanna 990 patent (KhaX 2001 at col. 44), and by Table 3 of the Kimura 858 patent (KhaX 2002, col. 63). Kimura's principal argument against Khanna's contention that its claimed compounds have unexpectedly higher activity than the prior art GPC-0 compound appears to be that the assays conducted by Gierse have such a low degree of accuracy and reproducibility that no reasonable comparisons may be made on the basis of the test results. Kimura cites as evidence a factor of 70-fold difference in data (IC_{50}) for the same compound (Compound 10, GPC-0). (Paper 36 at 9, citing "KM4, last sentence [sic]," which cites Gierse deposition testimony, KimX 1025 at 149, ll. 7-12, noting

[13] Khanna's expert Smith testified that in vitro COX-2 inhibition and selectivity does not always correlate with good analgesia activity (KimX 1026 at 53) or with good anti-edema activity (*id.* at 54).

reported COX-1 to COX-2 inhibition ratios ranging from 7 to 350.) ("KM4" denotes Kimura fact 4, in Paper 36 at 3-4.) Earlier sentences in KM4 cite other passages, specifically KimX 1025 at 137, l. 12 to 142, l. 3, at 142, ll. 5-10 and ll. 15-20. Examination of these passages indicates that this portion of the deposition related to Gierse's statement in his declaration that:

> [t]he IC_{50} values in Table 1 below for the Khanna (KHA) compounds are consistent with the corresponding values reported in Khanna U.S. Patent 5,935,990 at column 44, Table II (Khanna Ex. 2001). The IC_{50} values in Table 1 below for GPC-0 are consistent with the corresponding values reported in Kimura U.S. Patent 5,908,858 at column 63, Table 3 (Khanna Ex. 2002).

(KhaX 2037 at 6, ¶9, underscore added.) Gierse explained that, in characterizing IC50 values for KHA-10 that varied by a factor of 70 (IC50 = 10.2 in the 990 patent, IC50 = 0.137 in the Gierse declaration) as "consistent," he meant that the results of the Khanna 990 tests and his own tests indicated that the compound inhibited the COX-2 enzyme:

> Q (By Mr. Sweeney) Didn't your declaration say that your values were consistent with the Khanna patent?
>
> A Oh, I'm sorry. Consistent with the data in the Khanna patent?
>
> Q Right.
>
> A It's consistent in that it is a COX-2 inhibitor.

(KimX 1025 at 141, ll. 2-9.)

Counsel for Kimura was not satisfied:

Q But the values are not consistent between what's on the data sheet for the Khanna patent and the results of your testing, correct?

A Not in absolute – yes, they are, according to my determination, they were consistent.

Q You think a 70-fold difference in IC50 is consistent?

A These were ends of one done 13 years apart by two different – there's no statistics on these numbers. Each of these numbers were generated separately, like I said, at least 10 years apart by two different people.

Q Well, when you get data that has 70-fold difference in the same test in the same compound, do you think that's consistent or not?

A I determined that these were COX – these were indeed COX-2 inhibitors based on these two tests.

(KimX 1025 at 141, l. 10, to 142, l. 3.) Up to this point, Gierse has used the term "consistent" to characterize his interpretation that the two experiments both showed that the tested compound was a COX-2 inhibitor.

Still not satisfied, counsel for Kimura continued:

Q I'd like an answer to my question. When you get data for the same compound on IC50s, that has a 70-fold difference, do you think it's fair to represent that as consistent?

A We've seen differences in the same compound this large. These numbers can be without replicates and without statistics.

Q Can you answer my question yes or no?

A It would take further investigation to get more consistent numbers.

Q Can you tell me whether or not a 70-fold difference in IC50 for the same compound is consistent, in your view? Yes or no?

A I've seen this big a difference in compounds in the same assay run just about at the same time.

Q And you would report that to your supervisor as consistent data?

A It would be - it would be needed to be repeated additionally.

(KimX 1025 at 142, ll. 4-24.) Here, the questioner and Gierse have shifted the use of the term "consistent" to a discussion of the reproducibility of the test.

We observe that the Gierse article[14] (KimX 1016) states that there are many methods of assaying for IC_{50} values of COX inhibitors, and many variables, including the source of enzyme activity due to species variability[15], the use of recombinant enzymes[16], the method of analyzing for the product, and which product or reactant is used to monitor the course of the

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[14] James K. Gierse et al., *Kinetic basis for selective inhibition of cyclo-oxygenases*, 339 BIOPHYS. J. 607 (1999).

[15] Kimura, in its 858 patent, reported using COX-1 derived from ram seminal vesicles. (KhaX 2002 at 63, ll. 9-11.)

[16] The Gierse declaration (KhaX 2037 at 3-4, ¶6), the 990 patent (KhaX 1001 at col. 43, ll. 20-50), and Kimura's 858 patent (COX-2 tests) (KhaX 2002 at 63, ll. 11-16), all reported using recombinant COX-2 enzymes.

reaction. (KimX 1016 at 607, col. 2, and at 609, col. 2.) Moreover, the Gierse article indicates that the mechanism of inhibition is different for the two COX enzymes. As pointed out by Kimura in its deposition of Gierse, the final two sentences of the Gierse article read:

> Finally, for inhibitors that display distinct mechanisms of inhibition of COX-1 and COX-2, calculation of a selectivity ratio based on IC_{50} determinations is not supportable, since there are no underlying kinetic constants that are common to each isoform. This points to the need for analysis of selectivity *in vivo* under physiologically relevant conditions. [KimX 1016 at 613, col. 2.]

When asked to explain these sentences, Gierse stated:

> That is basically a statement . . . [that] enzyme assays can be configured in such a way that – to give widely varying potency in ratios.
>
> This was actually a paper that would suggest that the assay we were using for celecoxib was – was – was giving us ratios in COX-1/COX-2 inhibition that could be supported by the underlying kinetics.
>
> However, due to the fact that there are kinetic differences between inhibition of COX-1 and COX-2, that the real – that – that an additional determinant of selectivity would be in vivo. [KimX 1025 at 96, l. 25 to 97, l. 14.]

Taking all of these factors into account, we find that one skilled in this art would treat IC_{50} values cautiously, taking care to limit the conclusions one might draw, particularly from comparisons of values reported by different assays in different laboratories. Even when the same general assay is used, the record indicates that differences in procedures and details, such

as pre-incubation times or the activity of the specific batch of COX-1 or COX-2 enzyme, can lead to different results. Thus, we find credible Gierse's explanation that his results are "consistent" with the 990 patent results in that both show that compound KHA-10 are COX-2 inhibitors. We do not, however, on the basis of the evidence considered thus far, find any basis to question the reliability of the results reported in the Gierse declaration, aside from his statement, quoted *supra*, that "I've seen this big a difference in compounds in the same assay run just about at the same time." (KimX 1025 at 142, 18-20.) Kimura has not directed our attention to any particular data that indicates that the results reported in Table 1 of the Gierse declaration have, or are likely to have, COX inhibition values for the same compound acting on the same COX enzyme that differ by as much as 70 μM.

Gierse testified that the data reported in table 1 (KhaX 2037 at 7) were collected using a standard COX-1/COX-2 recombinant enzyme assay that had been used in his laboratory for about ten years. (KhaX 2037 at 2, ¶3; KimX 1015 at 57, ll. 4-7.) The experiments were run over two days (KimX 1025 at 63, ll. 18-19) on three sample plates, each plate having five test samples (KimX 1025 at 57, ll. 7-8), as well as a negative control (no enzyme), a positive control for enzyme activity, and a

positive control for inhibition (KimX 1025 at 58, ll. 10-24.) Recombinant human COX-1 and COX-2 enzymes (hCOX-1 and hCOX-2) were used throughout, and seven different concentrations of compounds (each successively diluted by a factor of three) were tested for inhibiting activity, as measured by PGE 2 production (ELISA assay). (KhaX 2037 at 5, ¶¶ 7-8.) The tests were not repeated. (KimX 1015 at 62, ll. 6-7.) Therefore, the experimental error for these tests was not determined (KimX 1015 at 62, ll. 13-21), and the reproducibility of the results depends on an assumption that the reproducibility of results for other compounds can be transferred to these tests (KimX 1015 at 63, ll. 9-17.) Moreover, compounds 11-15 (KhaX 2016 at 16-18) were tested without an amethecin positive control for inhibition of both COX-1 (KimX 1015 at 79, l. 17, to 80, l. 3) and COX-2 (KimX 1015 at 82, ll. 1-17.) As a consequence, it cannot be determined from this plate whether compounds 11 to 15 are more or less active inhibitors of COX-1 (KimX 1015 at 81, ll. 19-24) or COX-2 (KimX 1015 at 83, ll. 2-8) than the indomethacin control. According to Gierse, however, the indomethacin control is an assurance that the assay worked – a check that is redundant if, as in this case, there are compounds on the plate that inhibited the enzyme. (KimX 1015 at 81, ll. 9-17.)

An example of the limited sort of qualitative conclusions

that can, according to Khanna's expert Gierse, be drawn reliably from his data, is provided by the following testimony from his deposition:

> Q And looking at the first box under redacted [Gierse notebook, KhaX 2016 at 12, data for compound 2]?
>
> A Yes.
>
> Q The – the slope of that curve is – appears to be less than the slope of the curves for the two graphs under that. Correct?
>
> A It is – it does not – it does not go to 100 percent. I'm sorry, it does not – it does not go to 100 percent, what we considered 100 percent inhibition.
>
> * * *
>
> Q So compound No. 2 did not have a very strong COX-2 inhibition, correct?
>
> * * *
>
> A It – it had – it inhibited COX-2.
>
> Q But to a greatly lesser extent than compounds 3 and 4. Correct?
>
> * * *
>
> A I – um, the absolute potency of this compound would have been a little bit less. <u>In this particular assay</u>.

(KimX 1025 at 72, l. 17 to 73, l. 5; objections omitted; underscore added.) Thus, Gierse was willing to make comparisons of the relative inhibition caused by compounds within this assay,

but he was reluctant to characterize the magnitude in more exact terms.

Notably, Kimura has not directed our attention to any testimony or argument that the data presented in Gierse Table 1 (KhaX 2037 at 7) were obtained in a manner inconsistent with accepted practices. Nor does Kimura point to any inconsistencies in IC_{50} data within Table 1. Moreover, Kimura does not point to "inconsistencies," except for absolute magnitude, between IC_{50} values reported in Gierse, in Khanna 990, or in Kimura's own involved application (see the 858 patent, KhaX 2002 at col. 63, Table 3). Every sample, except for GPC-0, shows 50% or greater inhibition of COX-2 at some concentration of test compound; and every sample, except for GPC-0, shows less inhibition of COX-1 over the measured range of concentrations.

Consistently, Gierse also testified that "[e]ach sample was tested in duplicate." (KhaX 2037 at 5, ¶7.) We observe that many "double" dots are visible in the plots in KhaX 2016 at pages 11, 12, 15, 17, and 18. These double dots are plotted at the same concentration, one above the other on the graphs, and are fairly close to one another on the Y-axis, which represents the percent of the inhibition activity of the control (KimX 1025 at 74, ll. 16-17). All of the plots are fairly smooth, in that either the upper or the lower dot could be taken at any

concentration, and the over all shape of the plot would not be strikingly different. We find that in those cases in which a large difference in inhibition is seen on going from lower to higher concentrations of test compound, that difference would be seen with points selected randomly from either the higher or lower of each pair of points. The doubled dots appear to correspond to the duplicate tests, and thus, they appear to provide a rough measure of the reproducibility of the assay when conducted with the same materials, at the same time, on the same sample plate. In no case is there any indication that significantly different values of IC_{50} would be obtained from the duplicate runs.

Our review of Gierse's declaration, deposition, and the Gierse article (KimX 1016), as well as the Khanna 990 and Kimura 898 patents, does not persuade us that Kimura's concerns are as damaging as Kimura argues. On the basis of these facts, we conclude that the data in Table 1 of the Gierse declaration (KhaX 2037 at 7) can be used for limited purposes. In particular, the relative activity of compounds tested on the same plate, and to a lesser extent, the relative activity of all compounds tested on the three plates, can be compared with reasonable confidence when the differences in IC_{50} are large, provided that fine distinctions are not attempted. In

particular, IC_{50}(hCOX-1) is greater than 100 µM for compounds KHA-1, KHA-8, KHA-10, KHA-13, KHA-18, KHA-22, KHA-24, and GPC-0. This means, roughly, that the inhibition of COX-1 activity at a test compound concentration of 100 µM was less than 50%. For all seven of the Khanna compounds, IC_{50}(hCOX-2) is less than 10, and for four of the Khanna compounds, IC_{50}(hCOX-2) is less than 1.0. The value of IC_{50}(hCOX-2) for GPC-0 is greater than 100 µM. Thus, following Griese's analysis of the relative inhibition abilities of Khanna compounds 2, 3, and 4, noted *supra*, we are comfortable in finding that each of these seven Khanna compounds, within the concentration range tested, inhibits COX-2 activity more than it inhibits COX-1 activity. The remaining Khanna compounds, namely, KHA-9, KHA-11, and KHA-20, have smaller IC_{50}(hCOX-1) values of approximately 39, 22, and 6 µM, respectively. Given the "consistency" of the IC_{50} values reported in the 990 patent and Gierse Table 1 – by which we mean that in each case the IC_{50} value for COX-1 is greater than for COX-2 by at least a factor of about 40, coupled with the simultaneous determination of these IC_{50} values with the other IC_{50} values reported in the table, we also find that these Khanna compounds have a greater influence on COX-2 activity than on COX-1 activity, at the recorded concentrations.

We are aware that, as Kimura urges, Khanna has not come

forward with expert testimony regarding the COX-2 selectivity of the seven Khanna compounds at issue in this motion. (Paper 36 at 9.) We also note, however, that Kimura's 858 patent indicates selectivity on the basis of the ratio of IC_{50} for COX-1/COX-2, and states that "[i]n this test, the compound of the present invention exhibited excellent inhibitory effects selective for cyclooxygenase-2." (KhaX 2002 at col. 63, Table 3, and ll. 58-60.) Review of the reissue application file shows that this language remains in the reissue application. Moreover, Kimura has not directed our attention to any statements by its experts regarding the meaning of IC_{50} ratios. Thus, the Gierse article appears to caution against over-interpreting IC_{50} ratios, especially against indiscriminate comparisons between different assays or between very different compounds with the same assay. In the present case, the applications of both parties indicate that those skilled in the art expected structurally similar compounds to have similar COX-inhibition properties. The weight given to such expectations depends, however, on the supporting experimental evidence. In this case, Khanna, via its expert Gierse, has come forward with sufficient evidence to show that the seven Khanna compounds have, compared to GPC-0, greater inhibition activity against COX-2.

We agree with Kimura that Khanna has not shown that GPC-0

lacks COX-2 selectivity. That is, we cannot say with much confidence that GPC-0 inhibits COX-1 or COX-2 at any concentration, although there is a single point, as noted by Kimura, that is not inconsistent with some inhibition.[17] We further agree with Kimura that Khanna has not come forward with expert testimony that the test results show that the compounds are COX-2 selective.[18] The continuing presence, in Kimura's involved reissue application, of statements that "in this test [reported in the 858 patent at col. 63, Table 3, KhaX 2002], the compounds of the present invention exhibits excellent inhibitory effects selective for cyclooxygenase-2," lead us to conclude that, at the time the invention was made, IC_{50} ratios were regarded by those skilled in the relevant arts as reasonably reliable indicators of COX-2 selectivity. The Kimura inventors attested that they had read and understood the application that led to the 858 patent, and they have not identified that statement as an error in the involved application. Gierse's

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[17] See KhaX 2016 at 15, lowest graph. Gierse denied, however, that any conclusion about COX-2 inhibition could be drawn from this single point: "Based on a single point, I could not make a determination whether this was even possible that it's COX-2 selective." (KimX 1025 at 115, ll. 20-22.)

[18] It appears that the work reported in *Gierse 1999*, which post-dates Khanna's filing date by more than a year, led Gierse to challenge some of the previously accepted uses of the term "COX-2 selective," and methods of assessing COX-2 selectivity based on IC_{50} ratios. As such, this paper has little value in determining what those skilled in the art would have considered COX-2 selective at the time Khanna's invention was made.

paper, particularly when explained by Gierse's deposition testimony, does not teach that the IC_{50} ratio is inconsistent with COX-2 selectivity, but rather that the reaction mechanisms *in vitro* are complicated, and the *in vivo* mechanisms are even more complicated, so the IC_{50} ratios must be used with care.

We turn now to the *in vivo* evidence that Kimura argues supports its conclusion that the Khanna compounds have no unexpected properties. Although the parties do not appear to dispute the conclusion that the positive signal of pain inhibition by the KHA-9 compound is an unexpected result, they disagree about the significance of the null results from the remaining Khanna compounds. The difficulty, according to Khanna, is that there are many reasons why a given compound might not exhibit a significant level of pain relief when administered orally. In sum, Khanna argues that the "bioavailability," that is, how much of the compound is available to inhibit the COX-2 enzyme in the test animal, is subject to so many variables that failure to observe pain relief cannot be attributed simply to the differences in the ability of the test compounds to interfere with the COX-2 enzyme. Kimura's reply, that the *in vivo* tests on which it relies are "standard," and that Khanna is willing to rely on them when the results are positive for inhibition, does not address the significance of the null result. To take one

simple example, the test animals may not have had relief from pain or swelling because too little compound was absorbed from the gut into the blood stream; another mode of administration might have avoided this problem.

While bioavailability and plasma levels are arguably properties of the compounds that cannot be ignored, they also reflect properties of the test animals – more precisely, these properties relate to the interactions of complicated organic compounds with extremely complicated living beings. Evidence of unexpected results must be commensurate in scope with the claims. *E.g., In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056, 1058 (Fed. Cir. 1990). If the present claims were limited to methods of relieving pain and swelling without gastric upset by oral administration of the compounds, Kimura's arguments, that its *in vivo* results are dispositive and that the *in vitro* results are irrelevant, might have more weight. Kimura, however, has chosen to attack the patentability of Khanna's claims on the basis of the alleged obviousness of the compounds to which Khanna's broadest claims are drawn. Broader claims admit of a wider range of evidence of unexpected results than narrower claims.

We find Khanna's evidence of unexpected results credible. Khanna's results relate to the molecular basis for the pharmacological efficacy of the claimed compounds. Moreover,

Khanna's results are based on a test that those skilled in the art, including Kimura, relied upon at the time the invention was made. We find further that skilled workers continue to rely on these tests, albeit more guardedly, now that the mechanisms and kinetics of action are better understood. Thus we credit Khanna's demonstration that its compounds are much stronger inhibitors of COX-2 than the reference compound GPC-0, and that its compounds, at low doses, inhibit COX-2 more than they inhibit COX-1. We also find Kimura's evidence of no unexpected results credible: none of the disputed compounds showed significant pain or swelling relief in oral administration studies in rats. Kimura's studies, however, involve interactions in extremely complicated systems, and there are many reasons why the rats might not have responded positively to the administered compounds. Although the absence of more controls may not weaken the conclusions that might be drawn from a positive showing of inhibition of pain and swelling, that absence seriously weakens the conclusions that can be drawn from a negative showing of no pain or swelling inhibition. Accordingly, we find Khanna's results more weighty than Kimura's results, and we hold that Khanna has rebutted Kimura's *prima facie* showing of obviousness of certain compounds within the scope of Khanna's claims.

Kimura preliminary motion 2 is DENIED.

In view of the denial of this motion, Kimura's concession that claims broad enough to read on Khanna compounds held obvious over the prior art will be amended to exclude such unpatentable compounds (Paper 36 at 7) is moot for the purposes of this interference.

Kimura preliminary motion 3

30. Kimura moves under 37 CFR § 1.633(c)(4) to redefine the interfering subject matter by designating Kimura claims 20, 23, 48, 51, 57, 60, 66, 69, 75, and 78 as not corresponding to the Count. (Paper 27 at 1.)

31. Kimura claim 20 reads:

1-(4-Ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole.

a. The compound of claim 20 is designated "KMR-67" in the briefs and exhibits submitted by Kimura.

b. Kimura claims 48, 57, 66, and 75 are directed to methods of treating or relieving a condition in a mammal, or inhibiting an activity in a mammal, by administering the compound of claim 20.

32. Claim 23 reads:

2-(3,4-Dimethylphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole.

a. The compound of claim 23 is designated "KMR-78" in the briefs and exhibits submitted by Kimura.

b. Kimura claims 51, 60, 69, and 78 are directed to methods of treating or relieving a condition in a mammal, or inhibiting an activity in a mammal, by administering the compound of claim 23.

33. Kimura concedes, for the purpose of this motion, that the compounds of Kimura claims 20 and 23 are *prima facie* obvious. (Paper 27 at 8.)

34. Kimura argues, however, that the compounds of claims 20 and 23 are nonobvious due to unexpected results in *in vivo* experiments. (Paper 27 at 8.)

a. With regard to analgesic activity, Kimura argues that its compounds have much higher efficacy ratios at much lower doses than do Khanna's compounds. (Paper 27 at 5, ¶III.11.)

b. With regard to anti-edema activity, Kimura argues that the ID_{30} value for KMR-67 is about 6× lower (more active) than KHA-11, the most active Khanna compound, while the ID_{30} value for KMR-78 is about 3× lower (more active) than KHA-11. (Paper 27 at 7, ¶III.15.)

35. Kimura rests the non-obviousness of the dependent claims on the non-obviousness of the independent compound claims 20 and 23. (Paper 27 at 8, ¶IV.1.(ii).)

36. Khanna compounds KHA-8, KHA-9, KHA-10, and KHA-11 are recited in Khanna's involved 990 patent claim 4 (KhaX 2001 at

col. 48, ll. 37-43.)

37. Khanna claim 4 has been designated as corresponding to the Count.

38. Kimura compares the analgesic and anti-edema properties of compounds KMR-67 and KMR-78 with Khanna compounds KHA-8, KHA-9, KHA-10, and KHA-11.

Discussion

Kimura, as movant, bears the burden of proving that it is entitled to the relief it seeks. 37 CFR § 1.637(a); *Velander v. Garner*, 348 F.3d 1359, 1369-70, 68 USPQ2d 1769, 1777 (Fed. Cir. 2003). Here, Kimura must "[s]how that the claim does not define the same patentable invention as any other claim whose designation in the notice declaring the interference as corresponding to the count the party does not dispute." 37 CFR § 1.637(c)(4)(ii). The Board, in the Standing Order (Paper 2), §26(j), has interpreted this rule as requiring comparison with the opponent's corresponding claims, not its own corresponding claims.[19]

In the context of this motion, we understand Kimura's concession that its claims 20 and 23 are *prima facie* obvious

[19] Section 26(j) of the Standing Order reads in relevant part, "A party's Rule 633(c) preliminary motion seeking to have it[']s claim designated as not corresponding to a count shall establish that the claim covers an invention which is not the same patentable invention as any of the opponent's claim designated as corresponding to a count."

(Paper 27 at 8, ll. 3-4) to be a concession that the subject matter of Khanna's claims designated as corresponding to the Count renders obvious, *prima facie*, the compounds KMR-67 and KMR-78. Kimura seeks to rebut the conceded *prima facie* case of obviousness, by a showing of unexpected results. (Paper 27 at 8.) The burden is on Kimura to show that the unexpected results are commensurate in scope with the claimed invention. *In re Peterson*, 315 F.3d 1325, 1330-31, 65 USPQ2d 1379, 1383 (Fed. Cir. 2003), *quoting In re Greenfield*, 571 F.2d 1185, 1189, 197 USPQ 227, 230 (CCPA 1978) ("Establishing that one (or a small number of) species gives unexpected results is inadequate proof, for 'it is the view of this court that objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support.'") (*quoting In re Tiffin*, 448 F.2d 791, 792, 171 USPQ 294, 294 (CCPA 1971))"). In the present case, Kimura does not contest the correspondence of any of Khanna's designated claims. Thus, it follows that unexpected results for the two compounds must be evaluated with respect to the full scope of each of Khanna's claims.

Even if we were to agree, *arguendo*, that Kimura's evidence supports its position that its compounds have unexpected properties compared to the closest exemplifications within the scope of Khanna's involved claims in Khanna's 990 patent, that

would not complete our inquiry. Although such a showing might suffice to overcome a *prima facie* case of obviousness based on claims to Khanna compounds KHA-8, KHA-9, KHA-10, or KHA-11, the issue before us is whether that showing suffices to overcome the conceded *prima facie* case of obviousness over each of the corresponding Khanna claims. It is Khanna's *claimed subject matter*, not its disclosure, over which nonobviousness must be established. *Noelle v. Ledermann*, 355 F.3d 1343, 1352, 69 USPQ2d 1508, 1516 (Fed. Cir. 2004) ("A patentee's invention is only found in a patentee's claims, unless the patentee uses sufficient means-plus-function language to invoke 35 U.S.C. § 112, paragraph (6). Thus, if the Board is to compare two inventions, the Board must only compare the parties' claims.").

Khanna's corresponding compound claims 1-3 and 6-9 cover 1,2,4,5-tetrasubstituted pyrroles, each claim being generic to a large number of compounds having a large number of possible substituents comprised of various chemical groups. Khanna claim 4 is a "Markush"-type claim that names some 23 distinct compounds[20]. The formulas for these compounds contain a variety of substituents, including ketones, aldehyde, cyano, halogen,

[20] Each of the compounds named in Khanna claim 4 appears to correspond to an example compound the synthesis of which is reported in the specification, (KhaX 2001 at cols. 26-42) along with a test of the IC_{50} value for COX-1 and for COX-2 inhibition for all but one compound (*id.* at col. 44, Table 2).

phenyl ethers, alcohols, and esters, that are not represented among the four Khanna compounds Kimura chose to test. Kimura, however, has not directed our attention to any evidence or testimony that the four Khanna compounds it tested are fairly representative of the full scope of compounds recited in Khanna claim 4, let alone any of the broader claims. This is not the ordinary case in which the evidentiary basis of obviousness is clearly set out, and in which facts have been established regarding the teachings of the prior art, the differences from the claimed invention, motivations to select and combine various prior art teachings, and what one of ordinary skill in the art would have reasonably expected. Such facts might have guided our deliberations; but they are absent. Kimura's argument, in its reply, that "[t]he working examples of the Khanna patent should include the best embodiments of the invention known to the inventors" (Paper 37 at 3), is inapposite. Disclosure of the best mode is not an issue in the inquiry into obviousness. Moreover, in view of the "biological unpredictability" that Kimura apparently agrees is part of this art (Paper 36 at 6, last paragraph, referring to the "different characteristics of the two position isomers" cited in Khanna's opposition 2, Paper 32 at 24), it is important that Kimura come forward with evidence that the compounds it uses to compare its own compounds with the genus

of compounds covered by Khanna's claims are representative of the genus as a whole. Kimura's assumption that the exemplified compounds are the best known compounds is not evidence.

Because Kimura failed to show unexpected results over the scope of Khanna's corresponding claims, Kimura preliminary motion 3 is DENIED.

IV. ORDER

In view of the foregoing considerations, it is:

ORDERED that Kimura preliminary motion 2 is DENIED;

FURTHER ORDERED that Kimura preliminary motion 3 is DENIED;

FURTHER ORDERED that a copy of this decision be given an appropriate paper number and entered into the file records of Khanna patent 5,935,990 and Kimura application 09/678,218;

FURTHER ORDERED that if there is a settlement, the attentions of the parties are directed to 35 U.S.C. § 135(c) and 37 CFR § 1.666.

JAMESON LEE
Administrative Patent Judge

SALLY GARDNER LANE
Administrative Patent Judge

MARK NAGUMO
Administrative Patent Judge

BOARD OF PATENT APPEALS AND INTERFERENCES

INTERFERENCE TRIAL SECTION

105,103
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